(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 002 794 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
24.05.2000 Bulletin 2000/21

(51) Int Cl 7: **C07D 211/22**, A61K 31/4465

(21) Application number: **99500208.6**

(22) Date of filing: **10.11.1999**

(84) *Designated Contracting States:*
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States
AL LT LV MK RO SI

(30) Priority: **18.11.1998 ES 9802420**

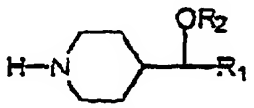
(71) Applicant: **FAES, Fabrica Espanola de Productos Quimicos y Farmaceuticos, S.A.**
48940 Lejona, Vizcaya (ES)

(72) Inventor. **FAES, Fabrica Espanola de Productos Quimicos y Farmaceuticos, S.A.**
48940 Lejona, Vizcaya (ES)

(74) Representative **Canadell-Isern, Roberto**
Po de la Castellana, 131 Bajo C
28046 Madrid (ES)

(54) 4-[(Aryl)(aryloxy)methyl]piperidine derivatives and their use as serotonin and/or noradrenaline reuptake inhibitors

(57) New 4-substituted piperidines of general formula (I) are described



(I)

in which groups R_1 and R_2 are non-substituted aryl radicals or aryl radicals mono- or poly-substituted with halogen (fluorine, chlorine, bromine, iodine), alkyl, alkoxy, cyano, trifluoromethoxy, trifluoromethyl, benzoyl, phenyl, nitro, amino, aminoalkyl, aminoaryl and carbonylamino

These compounds, and their pharmaceutically acceptable salts, inhibit serotonin and/or noradrenaline reuptake, and are useful as antidepressants Other potential therapeutic applications of these compounds are treatment of nervous bulimia, obsessive-compulsive disorders, alcohol addiction, anxiety, panic, pain, premenstrual syndrome and social phobia, as well as migraine prophylaxis.

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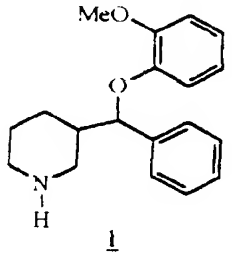
Printed by Jouve, 75001 PARIS (FR)

Description

Introduction

[0001] In recent years, selective serotonin reuptake inhibitors (SSRIs) have started to be used for treating depression and other central nervous system disorders, noteworthy among which are fluoxetine, citalopram. sertraline and paroxetine They all have different chemical structures, which helps to explain their different metabolic and phannacokinetic profiles Their performance as antidepressants compares with that of classic tricyclic compounds, but their advantage is that they are safer and better tolerated

[0002] The present invention relates to a number of new 4-substituted piperidines having an aryloxy functionality and potently inhibiting serotonin and/or noradrenaline reuptake, as a result of their high affinity for their neuronal transporters This characteristic provides them with an enhanced antidepressant potential in human therapy Other potential therapeutic applications of these compounds are treatment of nervous bulimia, alcohol addiction anxiety, obsessive-compulsive disorders, panic, pain, pre-menstrual syndrome and social phobia, as well as migraine prophylaxis Bibliography also describes other piperidine derivatives with aryloxy functionality as potential antidepressants albeit with a chemical nature differing essentially from those claimed herein, since the piperidine is substituted at the 3-position That is for instance the case of such compounds as 3-[(2-methoxyphenoxy)phenyl]methyl-piperidine 1 (Melloni P, Carniel, G , Della Torre, A , Bonsignalari, A , Buonamici. M., Pozzi, O Ricciardi S , Rossi, A C *Eur. J Med Chem. Chim. Ther* **1984,** 3. 235-242, Melloni, P, Della Torre, A , De Munari, S , Meroni, M . Tonani. R *Gazetta Chimica Italiana* **1985**, 115, 159-163) and 3-[(phenoxy)phenyl]methylpiperidine 2 (**FR 2,010,615** CA73, 66442j. **GB 1,203,149** CA73 120509b) In these compounds. the substitution of the piperidine ring at the 3-position results in an additional chiral centre The presence of the two chiral centres results in diastereomeric mixtures, which is the form in which the preparation of these compounds



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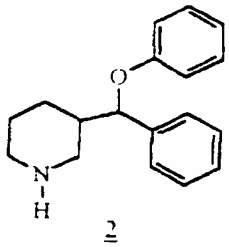

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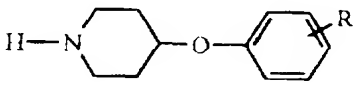
has been described The preparation and/or isolation of pure enantiomers is not described in any case However, the compounds claimed in the present specification possess a single chiral centre, since they have the piperidine ring substituted at the 4-position They have been prepared as racemic mixtures and as pure enantiomers, using synthetic methods differing from those used in preparing 1 and 2

[0003] Moreover, other piperidine derivatives having aryloxy functionality and the piperidine ring substituted at the 4-position have been described as potential antidepressants (formulae 3 and 4). Thus, in the case of 3 type compounds (**JP 96 40,999** CA124 343333n),



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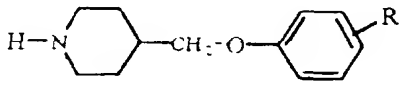

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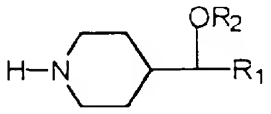
the aryloxy group is directly joined to the piperidine ring, whereas in the 4 type compounds (**JP 96 40,999** CA124 343333n) said group is joined to the piperidine ring through a methylene group which has no further substitutions The compounds described herein differ largely from those, since they have the aryloxy group joined to the piperidine ring through a methylene group wherein, in all cases, one of the methylene group hydrogens is substituted by an aryl group, substituted or not, as defined hereinafter These compounds are therefore structurally different from the 3 and 4 types and the synthetic methodology used in preparing the same is also absolutely different

Description

[0004] The new 4-substitude piperidines described in the present invention are represented by general formula (I), in which groups R_1 and R_2 are non-substituted aryl radicals or aryl radicals mono- or poly-substituted with halogen (fluorine, chlorine, bromine, iodine). alkyl, alkoxy, cyano, trifluoromethoxy, trifluoromethyl, benzoyl, phenyl. nitro, amino, aminoalkyl, aminoaryl and carbonylamino

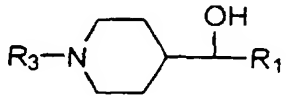


(I)

[0005] The compounds of general formula (I) have an asymmetric centre and have been prepared as racemic mixtures and as pure enantiomers The present invention includes all optical isomers of the compounds of general formula (I) and racemic mixtures thereof The present invention also comprises the pharmaceutically acceptable salts of these compounds with inorganic acids (such as hydrochloric, hydrobromic, nitric, sulphuric and phosphoric) and with organic acids (such as acetic, fumaric tartaric, oxalic, citric, *p*-toluenesulphonic and methanosulphonic)

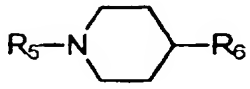
[0006] The racemic compounds of general formula (I) were prepared using well-known synthetic methods starting with the compounds of general formula (II)

[0007] Formation of the alkylarylether group was carried out using the Mitsunobu reaction (Mitsunobu, O *Synthesis* **1981**, 1, Hughes, D.L. *Organic Reactions 42,* 335) with phenols R_2-OH, in which R_2 is an aryl radical, substituted or not, as described for general formula (I), and the compounds of general formula (II), in which R_1 is an aryl radical, substituted or not, as described for general formula (I), and R_3 is hydrogen or R_4, which is an alkoxycarbonyl radical, preferably ethoxycarbonyl and t-butoxycarbonyl



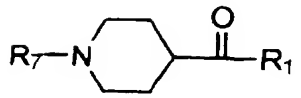
(II)

[0008] The alkylarylether group was also prepared using an aromatic nucleophilic substitution reaction (Berglund, R A. *Org. Proc. Res Dev* **1997** 1, 328-330) with the compounds of general formula (II) defined above, and the fluorinated derivatives R_2-F, in which R_2 is an aryl radical mono- or poly-substituted with halogen (fluorine, chlorine, bromine, iodine), alkyl, alkoxy, cyano, trifluoromethoxy, trifluoromethyl benzoyl, phenyl, nitro, amino, aminoalkyl, aminoaryl and carbonylamino. The compounds of general formula (II) were prepared using conventional synthetic methods. starting with the compounds of general formula (III) (Duncan. R L , Helsley G C , Welstead, W J , DaVanzo, J P , Funderburk, W.H., Lunsford, C.D *J Med. Chem* **1970**, 13 (1), 1), in which R_5 is an acetyl radical, ethoxycarbonyl and R6 is cyano or carboxy



(III)

[0009] The compounds of general formula (III) defined above were transformed into the compounds of general formula (IV), in which R_1 is an aryl radical, substituted or not,



(IV)

as described for the compounds of general formula (I), and R_7 is hydrogen, acetyl or R_4, which is an alkoxycarbonyl radical, preferably ethoxycarbonyl and t-butoxycarbonyl. Such transformation was made using two reaction types a) a Friedel-Crafts reaction of the acid chlorides derived from the compounds of general formula (III), in which R_5 is an acetyl or ethoxycarbonyl and R_6 is carboxy (Duncan, R L , Helsley, G C., Welstead, W.J , DaVanzo, J P Funderburk W H , Lunsford, C D. *J Med Chem* **1970**, 13 (1), 1) with benzene or conveniently functionalised derivatives thereof, or b) a Grignard reactive addition reaction, prepared from conveniently functionalised aryl halides, to compounds of general formula (III) in which R_5 is acetyl, ethoxycarbonyl or t-butoxycarbonyl and R_6 is cyano (Duncan, R.L , Helsley, G C , Welstead. W.J , DaVanzo, J P , Funderburk, W.H., Lunsford, C D *J Med. Chem.* **1970**, 13 (1), 1) Reduction of the compounds of general formula (IV) described provides the general formula (II) alcohols defined above.

[0010] The enantiomers composing the racemic mixtures of general formula (I) were obtained using two different pathways a) resolution of the corresponding racemic mixture by split crystallisation of the diastereomeric salts prepared with chiral acids (D or L-dibenzoyltartaric, D or L-tartaric, D or L-di-p-toluyltartaric and D or L-mandelic) and b) enantioselective synthesis In the latter case, the enantiomers of general formula (I) were obtained by reacting phenols R_2-OH or the fluorinated aromatic derivatives R_2-F defined above, with the enantiomers of the general formula (II) alcohols, as described for the racemic mixtures of general formula (I). In the enantiomers of the general formula (II) alcohols, R_1 is an aryl radical, substituted or not, as defined for the compounds of general formula (I), and R_3 is hydrogen or R_4, which is an alkoxycarbonyl radical, preferably ethoxycarbonyl and t-butoxycarbonyl. The enantiomers of the general formula (II) alcohols defined above were obtained by enantioselective reduction (Ramachandran, P.V., Teodorovic, A V, Rangaishenvi, M.V, Brown, H.C. *J Org. Chem* **1992**, 57, 2379-2386) of the compounds of general formula (IV) (Duncan, R L , Helsley, G C , Welstead, W J., DaVanzo, J P , Funderburk, W H , Lunsford, C D *J. Med Chem* **1970**, 13 (1), 1), in which R_1 is an aryl radical, substituted or not, as defined for the compounds of general formula (I), and R_7 is hydrogen or R_4, defined above.

[0011] The pharmacological activity of the compounds of general formula (I) was determined using well-established in vitro and in vivo pharmacological processes. The affinity of the compounds for the serotonin reuptake receptors (5HT) was evaluated in full rat cerebral cortex, using [^{3}H]-paroxetine as radioligand (Habert, E., Graham, D , Tahraoui. L , Claustre, Y , Langer, S Z. *Eur J Pharmacol.* 1985, 118, 107-114) yielding K_i values ranging between 0 5 and 500 nmol/l The affinity of the compounds for noradrenaline (NA) reuptake receptors was evaluated in full rat cerebral cortex, using [^{3}H]-nisoxetine as radioligand (Tejani-Butt, S.M , *J. Pharmacol. Exp. Ther.* **1992**, 260, 1, 427-436), yielding K_i values ranging between 1 and 500 nmol/l. The following were used as assays predicting antidepressant activity· mouse tail suspension (Stéru, L , Chermat, R., Thierry, B , Mico, J A , Lenégre, A., Stéru, M., Simon, P., Porsolt, R.D. *Prog Neurophsychopharmacol. Biol Psychiat.* **1987**, 11, 659-671), rat or mouse desperate behaviour (Porsolt, R.D , Anton G , Blavet, N., Jalfre, M *Eur. J Pharmacol.* **1978**, 48, 379-394) and enhancing rat yohimbine induced lethality (Quinton, R M *Brit. J Pharmacol.* **1963**, 21, 51-66) The compounds with K_i ranging between 0.5 and 40 nmol/l, for one of the transporters or for both, displayed an excellent antidepressant activity in the three models when administered within the 1 to 30 mg/Kg range orally, intraperitoneally or subcutaneously.

[0012] The following examples illustrate the scope of the present invention, which is not howsoever limited to such examples

Example 1

(+/-)-4-[(4-trifluoromethoxyphenoxy)-2-(4-fluorophenyl)]methyl-piperidine, fumarate

[0013] A mixture of (+/-)-4-[(4-trifluoromethoxyphenyl)hydroxy]methyl-1-piperidinecarboxylic acid, 1,1-dimethyl-ethylester (2 25 g, 7 27 mmol), 2-pyridyl-diphenylphosphine (1.90 g, 7.27 mmol) and 1 3 g (7 4 mmol) of 4-trifluoromethoxyphenol in 40 mL of tetrahydrofurane (THF) was treated with a solution of diethyl-aza-dicarboxylate (DEAD) (1 15 mL) in 10 mL of THF. The reaction mixture was stirred at 20°C for 4-6 h and concentrated. The residue was dissolved in ethyl ether, washed with an aqueous HCl (10%) solution and an aqueous NaOH (5%) solution, dried (anh Na_2SO_4), filtered and concentrated 2 4 g (71%) were obtained of an oil which was dissolved in dichloromethane (50 mL) and treated with a solution of trifluoroacetic acid (2 1 mL) in 10 mL of dichloromethane After 20 h at 20°C, this was washed

with an aqueous NaOH (5%) solution and saturated aqueous NaCl solution Drying (anh Na_2SO_4), filtering and concentration provided 1 3 g (71%) of the product, which was suspended in anhydrous ether (60 mL) and treated with fumaric acid (0.42 g), yielding 1 0 g of the fumarate (60% yield) with a m p = 130-134°C The RMN-^{1}H (DMSO-d_6) displayed a characteristic signal at 4 31 ppm (d J = 5 9 H_z, 1H, C<u>H</u>OAr) and RMN-^{13}C (DMSO-d_6) displayed at 74 9 ppm a signal corresponding to <u>C</u>HOAr carbon

Example 2

(+/-)-4-((4-fluorophenoxy)(4-fluorophenyl)]methyl-piperidine, hydrochloride

[0014] A mixture of (+/-)-4-[(4-fluorophenyl)hydroxy]methyl-1-piperidinecarboxylic acid, 1,1-dimethyl-ethylester (16.33 mmol) and 1 9 g of 4-fluorophenol in 50 mL of THF was treated with 5.0 g of triphenylphosphine and a DEAD solution (3 45 mL) in 10 mL of THF was then added After 3 h, the solvent was distilled and the resultant oil was treated with hexane, yielding a precipitate which was filtered. The filtrate was concentrated and the residue dissolved in dichloromethane (100 mL) and treated with a trifluoroacetic acid solution (8 mL) in 30 mL of dichloromethane After 15 h, the reaction was worked as usual and the hydrochloride was prepared in THF, yielding 3 6 g thereof as an amorphous and slightly hygroscopic rose-coloured solid (Yield 70%) with a m p = 90°C (d) RMN-^{1}H ($CDCl_3$) of the hydrochloride displayed a characteristic signal at 4 72 ppm (d, J = 5.8 Hz, C<u>H</u>OAr) and RMN-^{13}C ($CDCl_3$) a signal at 83.1 ppm corresponding to <u>C</u>HOAr carbon

[0015] The following compounds were analogously prepared

(+/-)-4-[(4-fluorophenoxy)(4-chlorophenyl)]methyl-piperidine, hydrochloride (54% yield. hygroscopic),
(+/-)-4-[(4-methoxyphenoxy)(4-fluorophenyl)]methyl-piperidine, fumarate (60% yield, .p = 139-142°C),
(+/-)-4-[(4-trifluoromethylphenoxy)phenyl]methyl-piperidine, hydrochloride (36% yield, hygroscopic),
(+/-)-4-[phenoxy)(4-chlorophenyl)]methyl-piperidine, hydrochloride (72% yield, m p = 80°C (d)),
(+/-)-4-[(4-benzoylphenoxy)phenyl]methyl-piperidine, hydrochloride (74% yield, m.p. 70°C (d)),
and (+/-)-4-[(4-trifluoromethoxy)phenyl]methyl-piperidine, fumarate (58% yield, m p = 76°C (d)).

Example 3

(+/-)-4-[(4-fluorophenoxy)phenyl]methyl-piperidine, sulfate

[0016] An NaH (1 95 g, 60% mineral water) suspension in 20 mL of dimethylsulfoxide (DMSO) was treated with a solution of (+/-)-4-(phenylhydroxy)methyl-1-piperidinecarboxylic acid, 1,1-dimethyl-ethylester (13.8 g, 47 mmol) in 36 mL of DMSO Potassium benzoate (7 5 g, 47 mmol) and 1 4-difluorobenzene (6 1 mL, 56 mmol) were added, and the reaction mixture was heated to 85°C until the starting substance disappeared. This was then treated with saturated aqueous NaCl and water solution, and extracted with ethyl ester. The organic phase evaporation residue was treated with methanol (200 mL) and aqueous HCl (10%, 200 mL) solution and refluxed for an hour The product was isolated with the usual methodology, yielding an oil (9 6 g, 72% yield) RMN-^{1}H ($CDCl_3$) displayed a signal at 4.70 ppm (d, J = 7.1 Hz, C<u>H</u>OAr) and RMN-^{13}C ($CDCl_3$) a signal at 85.0 ppm corresponding to <u>C</u>HOAr carbon The oil was treated with a 1 85 mL conc. H_2SO_4 solution in 90 mL of water, yielding the sulfate as a solid with a m p = 118-120°C (75% yield).

Example 4

(+/-)-4-[(3-fluorophenoxy)phenyl]methyl-piperidine, sulfate

[0017] An NaH (0.40 g, 60% mineral water) suspension in 6 mL DMSO was treated with a solution of (+/-)-4-(phenylhydroxy)methyl-1-piperidinecarboxylic acid, 1,1-dimethyl-ethylester (2 55 g, 8.75 mmol) in 6 mL of DMSO. Potassium benzoate (1 35 g, 8.43 mmol) and 1.3-difluorobenzene (1.05 mL, 10 6 mmol) were added, and the reaction mixture was heated to 85°C until the starting substance disappeared. It was then treated with saturated aqueous NaCl and water solution, and extracted with ethyl ester. The organic phase evaporation residue was treated with methanol (30 mL) and aqueous HCl (10%, 30 mL) solution and refluxed for an hour. The usual reaction working process yielded 2 16 g of an amber oil (88% yield) RMN-^{1}H ($CDCl_3$) displayed a signal at 4 78 ppm (d, J = 6 4 Hz, 1H, <u>C</u>HOAr) and RMN-^{13}C ($CDCl_3$) a signal at 84 6 ppm corresponding to CHOAr carbon. The oil was treated with a 0 20 mL conc. H_2SO_4 solution in 10 mL of water, yielding the sulfate as a solid with a m p = 72-76°C

[0018] The following compounds were analogously prepared

(+/-)-4-(phenoxyphenyl)methyl-piperidine, hydrochloride (73% yield, hygroscopic),

(+/-)-4-[(4-cyanophenoxy)phenyl]methyl-piperidine, fumarate (81% yield, m.p = 76°C (d)),
(+/-)-4-[(3-trifluorophenoxy)phenyl]methyl-piperidine, hydrochloride (72% yield, m p = 58°C (d)),
(+/-)-4-[(4-bromophenoxy)phenyl]methyl-piperidine, sulfate (70% yield, m p. = 99-103°C),
(+/-)-*N,N*-dimethyl-4-[[(4-piperidinyl)phenyl]methyl]oxy-benzamide, hydrochloride (72% yield, m p = 45°C (deliquescent)),
(+/-)-4-[(4-nitrophenyloxy)phenyl]methyl-piperidine, hydrochloride (80% yield, m p = 80°C (d)),
(+/-)-4-[(4-chlorophenyl)(1-naphthyloxy)]methyl-piperidine, sulfate (72% yield, m p = 186°C (d)),
(+/-)-4-[(1-naphthyloxy)phenyl]methyl-piperidine, sulfate (70% yield, m p = 152°C (d))
(+/-)-4-[(2-fluorophenoxy)phenyl]methyl-piperidine, sulfate (72% yield. m.p. = 76°C (d)),
(+/-)-4-[(3-cyanophenoxy)phenyl]methyl-piperidine, hydrochloride (80% yield, m.p = 82°C (d)),
(+/-)-4-[(3-chlorophenoxy)phenyl]methyl-piperidine, sulfate (60% yield, m.p. = 101-104°C),
(+/-)-4-[(2-trifluoromethylphenoxy)phenyl]methyl-piperidine sulfate (80% yield. m p = 110°C (d)),
(+/-)-4-[(2-cyanophenoxy)phenyl]methyl-piperidine, oxalate (80% yield, m.p. = 105°C (d)),
(+/-)-4-[[(2-biphenyl)oxy]phenyl]methyl-piperidine, hydrochloride (84% yield, m.p = 84-87°C),
(+/-)-4-[[(4-biphenyl)oxy]phenyl]methyl-piperidine, hydrochloride (82% yield, m p = 130°C (d)),
(+/-)-4-[(3-bromophenoxy)phenyl]methyl-piperidine, sulfate (75% yield, m p = 98°C (d)),
(+/-)-4-[(4-iodophenoxy)phenyl]methyl-piperidine, sulfate (57% yield, m.p = 105°C (d)),
(+/-)-4-[(3-iodophenoxy)phenyl]methyl-piperidine, sulfate (37% yield, m p. = 127°C (d)),
(+/-)-4-[(3 5-difluorophenoxy)phenyl]methyl-piperidine, sulfate (86% yield, m.p. = 206-208°C),
(+/-)-4-[(3-fluoro-2-methylphenoxy)phenyl]methyl-piperidine, sulfate (80% yield, m.p = 125°C (d)),
(+/-)-4-[(3-chloro-4-cyanophenoxy)phenyl]methyl-piperidine, hydrochloride (70% yield, m.p = 125°C (d)).
(+/-)-4-[(5-chloro-2-methylphenoxy)phenyl]methyl-piperidine, sulfate (75% yield, m.p = 105°C (d)),
(+/-)-4-[(3-chloro-2-methylphenoxy)phenyl]methyl-piperidine, sulfate (89% yield, m.p. = 130°C (d)),
(+/-)-4-[(3 4-dichlorophenoxy)phenyl]methyl-piperidine, sulfate (91% yield, m p = 108°C (d)),
(+/-)-4-[(3-methoxy-5-fluorophenoxy)phenyl]methyl-piperidine, hydrochloride (65% yield, m p. = 200-203°C (d)), and
(+/-)-4-[(3-fluoro-5-cyanophenoxy)phenyl]methyl-piperidine, hydrochloride (76% yield, m.p = 70°C (d)),

Example 5

Resolution of (+/-)-4-[(3-fluorophenoxy)phenyl]methyl-piperidine

[0019] 4 45 g of L-(-)-dibenzoyltartaric acid were added over 7 1 g (25 mmol) of (+/-)-4-[3- fluorophenoxy)phenyl] methyl-piperidine dissolved in 175 mL of ethanol (96%) A white solid was obtained (m.p = 212°C (d)) which was treated with aqueous NaOH (5%) solution and extracted with chloroform, yielding the levorotary isomer (96% ee, m p = 59-62°C, $[\alpha]_{546}$ - 11 4, c = 0 576, $CHCl_3$).

[0020] The filtrate liquids obtained were concentrated and the free base was extracted by treatment with aqueous NaOH (5%) solution and chloroform The product obtained, dissolved in ethanol, was treated with D-(+)-dibenzoyltartaric acid using the preceding process A white solid was obtained (m.p. = 208°C (d)) which was treated with aqueous NaOH (5%) solution and extracted with chloroform, yielding the dextrorotary isomer (98% ee, m.p. = 59-62°C, $[\alpha]_{546}$ + 11 4, c = 0 618, $CHCl_3$)

[0021] The following compounds were analogously prepared

(+)-4-[(4-fluorophenoxy)phenyl]methyl-piperidine (96% ee, m p = 100-102°C $[\alpha]_{546}$ + 14, c = 0 259, $CHCl_3$)
(-)-4-[(4-fluorophenoxy)phenyl]methyl-piperidine (96% ee, m p = 100-102°C, $[\alpha]_{546}$ - 14, c = 0.237, $CHCl_3$)
(+)-4-[(4-trifluoromethylphenoxy)phenyl]methyl-piperidine, sulfate (96% ee, m.p = 85°C (d), $[\alpha]_{365}$ + 17.8, c = 0 556, $CHCl_3$)
(-)-4-[(4-trifluoromethylphenoxy)phenyl]methyl-piperidine, sulfate (96% ee, m.p = 85°C (d), $[\alpha]_{365}$ - 15 5 c = 0.508, $CHCl_3$)
(+)-4-[(4-bromophenoxy)phenyl]methyl-piperidine (96% ee m p = 129-131°C (d), $[\alpha]_{436}$ + 54, c =1 012,$CHCl_3$)
(-)-4-[(4-bromophenoxy)phenyl]methyl-piperidine (95% ee, m p. = 129-131°C (d), $[\alpha]_{436}$ - 54.1, c = 1 048, $CHCl_3$)
(+)-4-[(3-chlorophenoxy)phenyl]methyl-piperidine, methanosulfate (98% ee, m.p = 200-202°C (d), $[\alpha]_{365}$ + 14 6, c = 0 646, $CHCl_3$)
(-)-4-[(3-chlorophenoxy)phenyl]methyl-piperidine, methanosulfate (99% ee, m.p = 200-202°C (d), $[\alpha]_{365}$ + 13 6, c = 0 690, $CHCl_3$)
(+)-4-[(3-cyanophenoxy)phenyl]methyl-piperidine, hydrochloride (95% ee, m.p = 70°C (d), $[\alpha]_{436}$ + 26 5, c = 0 600, $CHCl_3$)
(-)-4-[(3-cyanophenoxy)phenyl]methyl-piperidine, hydrochloride (98% ee, m p = 70°C (d), $[\alpha]_{365}$ - 27 1, c = 0 680,

$CHCl_3$)
(+)-4-[(3,5-difluorophenoxy)phenyl]methyl-piperidine, sulfate (96% ee, m p = 78°C (d), $[\alpha]_{436}$ + 19 4, c = 0 80, $CHCl_3$)
(-)-4-[(3.5-difluorophenoxy)phenyl]methyl-piperidine, sulfate (98% ee, m.p = 78°C (d), $[\alpha]_{416}$ - 19 8, c = 0 724, $CHCl_3$)
(+)-4-[(3-fluorophenoxy)(3-fluorophenyl)]methyl-piperidine, hydrochloride (96% ee, m.p = 75°C (d) $[\alpha]_{546}$ + 15, c = 0 183, $CHCl_3$) and
(-)-4-[(3-fluorophenoxy)(3-fluorophenyl)]methyl-piperidine, hydrochloride (95 4% ee. m p = 78°C (d), $[\alpha]_{546}$ - 16, c = 0 17, $CHCl_3$)

Example 6

(+)-4-[(4-fluorophenoxy)phenyl]methyl-piperidine

[0022] 4-benzoyl-piperidine (2 0 g, 10 6 mmol) was added over a solution of 6 8 g of (+)-*B*-chlorodiisopinocanfeilb-oran ((+)-DIP-Cl) (21.25 mmol) in dichloromethane (20 mL, dry) cooled down to 3-4°C After reacting for 72 h 2 0 mL of acetaldehyde (35 46 mmol) were added and stirred at room temperature for 3 h. 24 mL of an aqueous NaOH (6N) solution dichloromethane and saturated aqueous NaCl solution were added. The phases were separated and the usual treatment of the organic phase provided (+)-α-phenyl-4-piperidinemethanol as a white solid with a m p = 64-66°C in a 90% yield (84% ee)

[0023] 1.8 g of aminoalcohol (+)-α-phenyl-4-piperidinemethanol (9 6 mmol) were dissolved in methanol (10 mL) The solution was cooled down to 0°C and a diterbutyl dicarbonate ($(Boc)_2O$) (2.5 g, 11.27 mmol) solution was added dropwise to 10 mL of methanol The mixture was stirred for 24 h at room temperature, the methanol was concentrated, water was added and extracted with dichloromethane. The usual treatment of the organic phase provided the desired alcohol as a slightly coloured oil in a 93% yield.

[0024] The alcohol prepared above (2.7 g, 9.3 mmol) dissolved in DMSO (25 mL) was added over an NaH (60%, 0 6 g) suspension in DMSO (5 mL) Potassium benzoate (1 53 g, 9 63 mmol) and 1,4-difluorobenzene (1.3 mL, 11 9 mmol) were added and the mixture was heated (70-75°C) until the starting substance disappeared. The reaction mixture was poured into water and saturated aqueous NaCl solution, and extracted with ether The oil obtained was refluxed with a mixture of methanol (40 mL) and an aqueous hydrochloric acid (40 mL) solution for 1h Isolation of the product using the customary methodology provided (+)-4-[(4-fluorophenoxy)phenyl]methyl-piperidine as an oil in a 54% yield Treatment of 0.5 g (1 75 mmol) of this oil with D-dibenzoyltartaric acid in ethanol (96%, 30 mL) provided a precipitate which was filtered (m.p = 198-199°C). The aminoether was released yielding a white solid with a 96% ee, m p. = 102-104°C and $[\alpha]_{546}$ + 15, c = 0.105, $CHCl_3$)

[0025] The following compounds were analogously prepared

(+)-4-[(4-nitrophenoxy)phenyl]methyl-piperidine, hydrochloride (96% ee, m.p = 55°C (d). $[\alpha]_{436}$ + 36, c = 0 045, Ethanol)
(-)-4-[(1-naphthyloxy)phenyl]methyl-piperidine, hydrochloride (98% ee, m.p = 65°C (d), $[\alpha]_{546}$ - 180, c = 0 080, $CHCl_3$) and
(+)-4-[(2-fluorophenoxy)phenyl]methyl-piperidine, sulfate (97.6% ee, m p = 105°C (d), $[\alpha]_{546}$ + 31, c = 0 081, $CHCl_3$).

Example 7

(-)-4-[(4-fluorophenoxy)phenyl]methyl-piperidine

[0026] 4-benzoyl-piperidine (7 35 g, 39.05 mmol) was added over a solution of 25 g of (-)-DIP-Cl (78.125 mmol) in dichloromethane (75 mL, dry) cooled down to 0-2°C After reacting for 72 h, 5 2 mL of acetaldehyde (92 2 mmol) were added and stirred at room temperature for 3 h. 71 mL of an aqueous NaOH (6N) solution, dichloromethane and saturated aqueous NaCl solution were added The phases were separated and the usual treatment of the organic phase provided (-)-α-phenyl-4-piperidinemethanol as a white solid with a m.p = 48-50°C in a 85% yield (86% ee). 2 g of aminoalcohol (-)-α-phenyl-4-piperidinemethanol (10 7 mmol) were dissolved in methanol (10 mL) The solution was cooled down to 0°C and a $(Boc)_2O$ (2.6 g, 11.73 mmol) solution was added dropwise to 7 mL of methanol. The mixture was stirred for 20 h at room temperature, the methanol was concentrated, water was added and extracted with dichloromethane The usual treatment of the organic phase provided the desired alcohol as a slightly coloured oil in a 90% yield

[0027] The alcohol prepared above (1 3 g, 4 5 mmol) dissolved in DMSO (10 mL) was added over an NaH (60%, 210 g) suspension in DMSO (5 mL) Potassium benzoate (715 g, 4 5 mmol) and 1,4-difluorobenzene (0 75 mL, 6 86

mmol) were added and the mixture heated (70-75°C) until the starting substance disappeared. The reaction mixture was poured into water and saturated aqueous NaCl solution, and extracted with ether The oil obtained was refluxed with a mixture of methanol (17 mL) and an aqueous hydrochloric acid (17 mL) solution for 1h The usual working of the reaction provided (-)-4-[(4-fluorophenoxy)phenyl]methyl-piperidine as an oil in a 64% yield Treatment of this oil with L-dibenzoyltartaric acid in ethanol (96%. 35 mL) provided a precipitate which was filtered (m p = 193-194°C) The aminoether was released yielding a white solid with a 98% ee, m.p = 100-102°C and $[\alpha]_{546}$ - 14 c = 0 2, $CHCl_3$)

[0028] The following compounds were analogously prepared

(-)-4-[(4-nitrophenoxy)phenyl]methyl-piperidine, hydrochloride (98 7% ee, m.p. = 59°C (d), $[\alpha]_{436}$ - 31, c = 0 042, Ethanol)
(+)-4-[(1-naphthyloxy)phenyl]methyl-piperidine, hydrochloride (94% ee, m.p. = 115°C (d), $[\alpha]_{546}$ - + 156, c = 0 128, $CHCl_3$) and
(-)-4-[(2-fluorophenoxy)phenyl]methyl-piperidine, sulfate (97 6% ee, m.p = 90°C (d), $[\alpha]_{546}$ - 31, c = 0 140, $CHCl_3$)

Example 8

(+/-)-4-[(3-fluorophenoxy)(3-fluorophenyl)]methyl-piperidine, sulfate

[0029] a mixture of 4-cyanopiperidine (5 g, 40.92 mmol), $(Boc)_2O$ (11 7 g, 53.7 mmol), sodium bicarbonate (11 7 g, 139.3 mmol) and water (117 mL) was stirred at room temperature for 17 h this was extracted with dichloromethane and the organic phase dried (anh. Na_2SO_4), filtered and concentrated. The resultant oil was purified by flash chromatography (Still W C , Kahn, M , Mitra, A. *J Org. Chem* **1978**, 43, 2923) yielding 4-cyano-1-piperidinecarboxylic acid, 1,1-dimethyl-ethylester as a yellow oil in a 43% yield

[0030] A Mg (0 5 g) suspension in ether (dry, 22mL) was treated with some millilitres (approximately ¼ of the total) of a 1-bromo-3-fluorobenzene (2 15 mL, 19 4 mmol) solution in ether (dry, 16 mL) and an iodine crystal. This was heated until a smooth reflux was observed and the colour disappeared The rest of the solution was then added dropwise maintaining a mild reflux. With the addition at an end, this was refluxed for 1 h 30 min and allowed to cool down to room temperature A 4-cyano-1-piperidinecarboxylic acid ,1,1-dimethyl-ethylester (2.7 g, 12 84 mmol) solution was added dropwise to dry ether (27 mL) and the resultant mixture refluxed for 3 h A saturated aqueous NH_4Cl (50 mL) solution was added and extracted with ether The usual treatment of the organic phase provided an oil which was purified by flash chromatography (Still, W C. Kahn, M., Mitra, A *J. Org. Chem* **1978**, 43, 2923) yielding 2.4 g (61% yield) of 4-(3fluorobenzoyl)-1-piperidinecarboxylic acid, 1,1-dimethyl-ethylester as a yellowish oil

[0031] The product obtained above (2.4 g, 7.8 mmol) was dissolved in methanol (30 mL) and $NaBH_4$ (0.2 g) dissolved in 3 5 mL water was added The mixture was heated for 2 h in an oil bath (50-60°C) and the product isolated in the usual manner, yielding (+/-)4-(3-fluorophenyl)hydroxy]methyl-1-piperidinecarboxylic acid, 1 1-dimethyl-ethylester as a very dense yellowish oil in quantitative yield

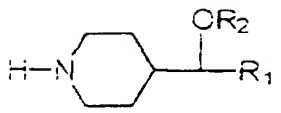
[0032] A solution of the racemic alcohol prepared above (2 4 g, 7.8 mmol) in DMSO (25 mL) was added dropwise to an NaH (60%) (0.62 g) suspension in DMSO (15 mL). Potassium benzoate (1.53 g, 9.55 mmol) and 1,3-difluorobenzene (1 2 mL, 11 9 mmol) were added and the mixture was heated in an oil bath (65-70°C) until the starting substance disappeared This was then poured into a mixture of saturated NaCl (50 mL) solution and water (39 mL). This was extracted with ether and the usual treatment of the ethereal phase provided an oil which was refluxed with a mixture of methanol (40 mL) and aqueous HCl (10 %, 40 mL) solution for 1 h 30 min The desired product (+/-)-4-[(3-fluorophenoxy)(3-fluorophenyl)]methyl-piperidine was obtained as an amber oil in a 50% yield RMN-^{1}H ($CDCl_3$) of this product displayed a signal at 4.55 ppm (d, J = 6 1 Hz, CHOAr) and RMN-^{13}C ($CDCl_3$) a signal at 83.9 ppm corresponding to CHOAr carbon. The oil prepared above was treated with a 0.22 mL conc H_2SO_4 solution in 16.5 mL of water, yielding the sulfate as a slightly coloured solid (m.p. = 158°C (d))

[0033] The following compounds were analogously prepared

(+/-)-4-[(2-fluorophenoxy)(3-fluorophenyl)]methyl-piperidine, hydrochloride (62% yield, m.p = 90°C) and
(+/-)-4-[(4-fluorophenoxy)(3-fluorophenyl)]methyl-piperidine, hydrochloride (30% yield, m.p = 65°C).

Claims

1. 4-substituted piperidines, of general formula (I), in which R_1 and R_2 are non-substituted aryl radicals or aryl radicals mono- or poly-substituted with halogen (fluorine, chlorine, bromine, iodine), alkyl, alkoxy, cyano, trifluoromethoxy, trifluoromethyl, benzoyl, phenyl, nitro, amino, aminoalkyl, aminoaryl and carbonylamino, and their pharmaceutically acceptable salts with inorganic acids and organic acids



(I)

2. In accordance with claim 1, the 4-substituted piperidines of general formula (I) obtained as racemic mixtures and as pure enantiomers

3. In accordance with claims 1 and 2, the 4-substituted piperidines of general formula (I) listed hereinafter, obtained as racemic mixtures or pure enantiomers, and their pharmaceutically acceptable salts

4-(phenoxyphenyl)methyl-piperidine,
4-[(4-fluorophenoxy)phenyl]methyl-piperidine
4-[(4-methoxyphenoxy)(4-fluorophenyl)]methyl-piperidine
4-[(4-fluorophenoxy)(4-fluorophenyl)]methyl-piperidine
4-[(4-fluorophenoxy)(4-chlorophenyl)]methyl-piperidine
4-[(4-trifluoromethylphenoxy)phenyl]methyl-piperidine
4-[(4-trifluoromethoxyphenoxy)(4-fluorophenyl)]methyl-piperidine
4-[phenoxy(4-chlorophenyl)]methyl-piperidine
4-[(4-benzoylphenoxy)phenyl)]methyl-piperidine
4-[(4-trifluoromethoxyphenoxy)phenyl]methyl-piperidine
4-[(4-cyanophenoxy)phenyl]methyl-piperidine
4-[(3-trifluorophenoxy)phenyl]methyl-piperidine
4-[(3-fluorophenoxy)phenyl]methyl-piperidine
4-[(4-bromophenoxy)phenyl]methyl-piperidine
N,N-dimethyl-4-[[(4-piperidinyl)phenyl]methyl]oxy-benzamide
4-[(4-nitrophenyloxy)phenyl]methyl-piperidine
4-[(4-chlorophenyl)(1-naphthyloxy)]methyl-piperidine
4-[(1-naphthyloxy)phenyl]methyl-piperidine
4-[(2-fluorophenoxy)phenyl]methyl-piperidine
4-[(3-cyanophenoxy)phenyl]methyl-piperidine
4-[(3-chlorophenoxy)phenyl]methyl-piperidine
4-[(2-trifluoromethylphenoxy)phenyl]methyl-piperidine
4-[(2-cyanophenoxy)phenyl]methyl-piperidine
4-[[(2-biphenyl)oxy]phenyl]methyl-piperidine
4-[(3-fluorophenoxy)(3-fluorophenyl)]methyl-piperidine
4-[(2-fluorophenoxy)(3-fluorophenyl)]methyl-piperidine
4-[(4-fluorophenoxy)(3-fluorophenyl)]methyl-piperidine
4-[[(4-biphenyl)oxy]phenyl]methyl-piperidine
4-[(3-bromophenoxy)phenyl]methyl-piperidine
4-[(4-iodophenoxy)phenyl]methyl-piperidine
4-[(3-iodophenoxy)phenyl]methyl-piperidine
4-[(3,5-difluorophenoxy)phenyl]methyl-piperidine
4-[(3-fluoro-2-methylphenoxy)phenyl]methyl-piperidine
4-[(3-chloro-4-cyanophenoxy)phenyl]methyl-piperidine
4-[(5-chloro-2-methylphenoxy)phenyl]methyl-piperidine
4-[(3-chloro-2-methylphenoxy)phenyl]methyl-piperidine
4-[(3,4-dichlorophenoxy)phenyl]methyl-piperidine
4-[(3-methoxy-5-fluorophenoxy)phenyl]methyl-piperidine, and
4-[(3-fluoro-5-cyanophenoxy)phenyl]methyl-piperidine.

4. Pharmaceutical compositions containing a therapeutically effective quantity of a compound of general formula (I) in accordance with the preceding claims, mixed with pharmaceutically acceptable excipients, to be orally, parenterally and topically administered

5. A method for treating central nervous system disorders in humans, particularly depression, nervous bulimia, obsessive-compulsive disorders, alcohol addiction, anxiety, panic, pain, pre-menstrual syndrome, social phobia and migraine prophylaxis, consisting of administering a therapeutically effective quantity of a compound of general formula (I) in accordance with the preceding claims

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which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 99 50 0208

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
D,Y	MELLONI P ET AL: "Potential antidepressant agents. Alpha-Aryloxy-benzyl derivatives of ethanolamine and morpholine" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY - CHIMICA THERAPEUTICA, vol. 19, no. 3, 1 January 1984 (1984-01-01), pages 235-242, XP000605241 ISSN: 0223-5234 * the whole document: in particular, page 238, table III: the compound no. 62; and page 239, column 1, lines 6-9 *	1-5	C07D211/22 A61K31/4465
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TECHNICAL FIELDS SEARCHED (Int.Cl.7)

C07D

INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

Although claim 5 is directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

Place of search	Date of completion of the search	Examiner
MUNICH	16 February 2000	Fink, D

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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Application Number
EP 99 50 0208

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
Y	CHEMICAL ABSTRACTS, vol. 106, no. 25, 22 June 1987 (1987-06-22) Columbus, Ohio, US; abstract no. 213767z, SUGIMOTO H ET AL: "Piperidine derivatives" page 645; column 2; XP002130615 * abstract; and Chemical Abstracts, CHEMICAL SUBSTANCE INDEX, vol. 106, 1987, page 7165CS, column 2, the first entry: the compounds with the RN: '107025-86-5! and '107025-85-4! * -& JP 61 227565 A (EISAI CO LTD) 9 October 1986 (1986-10-09)	1-5	TECHNICAL FIELDS SEARCHED (Int.Cl.7)

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ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 99 50 0208

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report
The members are as contained in the European Patent Office EDP file on
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16-02-2000

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82